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DEPARTMENT OF PEDIATRICS

630 West 168th Street

November 11, 1976

Jean D. Lockhart, M.D.
Director,
Department of Committees
American Academy of Pediatrics
P.O. Box 1034
Evanston, Illinois 60204

Dear Dr. Lockhart:

I wish to nominate Dr. Gerald Gaull for the Borden Award from the American Academy of Pediatrics for 1977. Although in recent years the Borden Award has been given "for outstanding research in the development of infants and children" earlier citations for this award focused more closely upon recognition of excellence in nutritional research. But whichever of these criteria is appropriate, I feel that Dr. Gaull's work eminently qualifies him for the award at this time.

By way of brief introduction to my evaluation of Gaull's work, let me sketch what I believe to have been the state of the problem of optimal protein intake for the low birth weight infant as of about 1970. This is the central question to which Gaull's research has provided important new answers, many of which have important ramifications to the areas of nutrition and metabolism in general.

Prior to the classic paper of Gordon and coworkers in 1947, feeding human milk with its low protein content to low birth weight infants was a very widespread practice. Gordon, however, showed that weight gain and nitrogen balance were significantly greater with 6.0 g/kg/d of protein than with human milk. As a result of this paper, the results of which were widely confirmed, feeding practices abruptly changed and low birth weight American babies were fed predominately high protein feedings for the next 15 or so years.

A few skeptics, however, took up the question originally posed by Gordon, namely that the augmented weight gain was really due to an increased ash intake rather than to the high protein intake, and there ensued a long series of papers over the next 20 years aimed at answering this question. These culminated in the paper by Babson and Bramhill in 1969 which showed that ash intake affected weight gain in the smallest, youngest infants and that all previous studies had shown this same effect to a statistically significant extent but only when this sub-group was separated out from the total.

It is curious that throughout the two decades following Gordon's paper, few if any investigators payed more than lip service to the quality as opposed to the quantity of protein. The problem seemed to be that no one seemed to take seriously the fact that cow's milk and human milk proteins might show subtle differences with respect to meeting the amino acid requirement for the low birth weight as opposed to the term infant. This was in fact to be the case, as Gaull's work would show.

Gaull came to this problem with an enviable record of earlier achievements (as documented in his bibliography), in studying problems involving the enzymatic basis of certain inborn errors of metabolism. As his C.V. demonstrates, he had general pathology and pediatric training in Boston and at our institution and further clinical training in pediatric neurology with Dr. Sidney Carter here and continued with biochemical training with Claude Villée, Charles Dent and Derek Richter.

Beginning in the mid-1960's, Gaull became deeply interested in the sulfur-containing amino acids and in the course of his studies on homocystinuria was led to look at cystathionase activity of human fetal liver and brain. He found that it was absent! This is a key enzyme in the transsulfuration pathway by which methinione is converted to cystine. As Gaull showed, because this enzyme is present in mature liver, methionine can be converted to cystine, and cystine is thus not an essential amino acid. But in the low birth weight infant with deficient cystathionase, these enzymatic observations implied that cystine was an essential amino acid for such infants; indeed this is part of the title of the now classic paper of Gaull et al. published in Science.

Two years later, Snyderman confirmed independently the essentiality of cystine for the LBW infant using the classical Holt-Snyderman design of feeding a diet deficient in a single amino acid and examining weight gain, nitrogen balance and plasma level. Unfortunately, Snyderman has never published these data in detail, perhaps because the whole design has been criticized on ethical grounds. But she has published enough data to provide definite confirmation of this postulate of Gaull.

Gaull next sought to examine the implications of his observations in an elegantly designed clinical study carried out in collaboration with Neils Raiha in Helsinki. I know the details of this study as well as both of the investigators quite well. I, therefore, think I can speak with some authority about the nature of their collaboration as well as about some of the elements of their study which are not known generally to the scientific community at large. Neils Raiha is a highly respected developmental biochemical pediatrician with a distinguished record of accomplishment on his own. In this particular collaboration, however, Neils was

not an equal intellectual partner with Gerry. Raiha did, however, have control of an extremely good nursery where the study was carried out. His well-trained nurses were absolutely compulsive about recording each of the many measurements specified by the protocol. They are also masters at collecting urine. Neils provided all the routine chemistry for the study; aliquots of each plasma and urine sample were frozen and returned to the U.S. to Gaull's lab where the amino acid analyses were carried out.

There is a series of four papers describing these results (copies enclosed). I have studied them all very carefully. They have now been accepted in final form; the first has been published and the others will be out within 6 months or so. The protocol called for random assignment of LBW infants in three gestational age categories to one of 5 feeding mixtures, either human milk or one of four artifical formulas delivering either 1.5 g% of protein intake or 3.0 g% protein intake. The quality of the protein in the formulas was either 60/40 or 18/82, lactalbumin to casein, at each of the two levels. The formulas provided exactly equivalent ash, vitamin, etc. intake. All 5 groups were fed isocalorically.

The first paper reported some of the overall results, the most important of which were that growth rate, measured either by body weight or by measures of linear growth (crown-rump or tibial length) were not different. But there were biochemical differences, in some cases related to quantity and in others, to quality of protein fed. Quantity effects confirmed previous work in a systematic way and were evident in BUN, total protein, albumin and globulin. Quality effects, however, concerned blood ammonia (a new observation), late metabolic acidosis (surmised but never proven by earlier work) and plasma tyrosine and phenylalanine (also suspected by previous work but never validated in as careful a manner).

It was with the sulfur-containing amino acids, however, that the most exciting new observations emerged and taken as a group along with parallel animal work by Gaull's laboratory, make him an outstanding nominee for the Borden Award.

The 18/82 infants had a low cystine intake and showed evidence of cystine depletion which was not seen in the 60/40 group, because of their cystine-rich lactalbumin intake. But cystine deficiency did not seem to impair overall growth as reflected by the growth data. One might at this point say "so what". It is true that on the high protein intakes, high plasma methionine and cystathinione (not usually measurable) levels were seen; all of these observations follow from the lack of cystathinionase activity.

But the cystine deficiency question and its apparent benign nature did raise some other questions and the answers were not long in coming. One important metabolite of cystine is taurine, that ubiquitious substance in plasma, urine and tissues which is first off the column and which most people, out of ignorance, have ignored.

Gaull's lab on the other hand had been interested in taurine for some time. They had shown that it was very high in fetal brain, decreasing linearly with time reaching the adult levels in 3 different species at the time of weaning. Furthermore, they showed that some of the high taurine concentration in fetal brain occurs because it is taken up by the developing synaptosomes, those peculiar vesicular structures at the ends of growing nerve. They also showed it was a specific mediator of axonal transport in gold fish optic nerve, thereby adding to the large body of data supporting the idea that taurine is an important neurotransmitter or neuromodulator and explaining why all excitable tissues including brain, nerve and cardiac and skeletal muscle show significant free taurine levels.

To return to the infants, those deficient in cystine were found to be deficient in taurine, as demonstrated by a fall in plasma and urine levels. But even those infants in the 60/40 group receiving an adequate cystine intake also showed taurine depletion. The reason for this is another observation of Gaull's that one of the enzymes which converts cystine to taurine, cysteine sulfinic acid decarboxylase, is markedly reduced (1/10th to 1/100th of other species) in mature human tissues and is virtually absent in the LBW infant.

But the denouement of this study was that infants fed human milk showed no evidence of taurine depletion because human milk contains abundant amounts of free taurine, a very old and heretofore unexplained observation. Taurine thus becomes an essential amino (sulfonic) acid for the LBW infant.

Thanks to this work, we now have a much better understanding of sulfur-containing amino acid metabolism and requirements for the LBW infant. The ultimate clinical significance of these observations remains to be worked out and that may take a very long time. But it is an intriguing problem. Could it be that some of the alledged long range benefits of human milk feeding to LBW infants with respect to mental and/or neurological status are really due to cystine or taurine rather than to protein per se? Could it be that there is a clinical abnormality waiting to be detected that corresponds to the severe retinal degeneration seen in the severely taurine deficient kitten? Is there a functional abnormality secondary to the taurine deficiency in limiting the secretion of taurocholic acid, the principal bile acid of early life?

This work of Gaull opens a whole new chapter in infant feeding. It represents a beautiful interaction of developmental biochemistry, neurochemistry and clinical nutrition. There is nothing like the prepared mind to see relationships that have been missed by others in this field for so long!

Undoubtedly this new work of Gaull will be taken out of context in the current indiscriminate surge towards feeding LBW infants human milk. This movement seems well underway having been instituted in the belief that fresh human milk confers protection of the infant against necrotizing enterocolitis. As the proponents of this approach mount their attack, it will be almost irresistible for them

to ignore these careful observations and to quote them out of context.

Further there is another controversy developing in which these data may be inaccurately quoted. The Iowa group has performed some interesting theoretical computations from the literature and have perfected a reference fetus. Their data show that human milk can't possible meet the protein requirement of such a fetus to sustain its growth on the 50th percentile level of the intrauterine rate. This has been loosely interpreted to mean that these infants on human milk will not grow. Yet Gaull's data show that they do grow! The resolution of this particular controversy is easy--the infants did not grow at the 50th percentile. Rather my calculations show they grew on the 25th percentile and at that rate, there is a reasonable efficiency of conversion of milk nitrogen (protein plus non-protein) to body nitrogen.

Neither of these issues should cloud the judgement of the committee as to the scientific merit of the nominee's accomplishments. They speak for themselves and they have many implications which all the rest of us will be exploring for years to come.

Sincerely yours,

Robert W. Winters, M.D.
Professor of Pediatrics

RWW:mln
Enclosures